B1

47. The method of claim 37 wherein said disease or condition is an autoimmune disorder.

48. The method of claim 37 wherein said disease or condition is psoriasis.--

REMARKS

By the present amendments, the previous claims have been cancelled in favor of new claims 37-48. The new claims emphasize that the subject therapies are for disease or conditions that involve an increased number of CD4 positive lymphocytes. Also, the claims have been rewritten to cover treatment of specific diseases and conditions finding explicit support at pages 64-65 of the application.

This amendment finds support e.g., at page 19, lines 30-32, page 20, lines 15-18, et al. Essentially, the therapeutic efficacy of the subject chimeric anti-CD4 antibodies resides in their ability to induce immunological non-responsiveness or tolerance by blocking the activity of cytotoxic CD4+ T lymphocytes. Many diseases, e.g., various autoimmune and non-autoimmune diseases are characterized by an increased number of cytotoxic T cells which can result in tissue destruction, inflammation, and other unwanted immune responses. The subject chimeric antibodies block these CD4+ T cell responses and thereby inhibit or reduce disease pathology, essentially by functioning as immunosuppressants and inhibiting inflammation, tissue destruction, and other aberrant immune responses associated with cytotoxic T cells.

Moreover, the subject antibodies, unlike other chimeric antibodies do not elicit a significant immune response, i.e., a HAMA response, because they contain variable regions derived from Old World Monkey antibodies, which, unlike rodent antibodies are highly similar to human antibody sequences, i.e., on the order of 90-92% identical, or greater.

Based on these properties, the subject antibodies are well suited for treating any disease involving cytotoxic (CD4+) T cells, and especially for the treatment of chronic conditions wherein repeated antibody administration is required. Essentially, the subject antibodies are suitable as they may be administered repeatedly without initiating an immune response. Indeed, they obviate problems associated with prior chimeric anti-CD4 antibodies, and are moreover significantly more easy to produce vis-à-vis humanized antibodies, since manufacture thereof does not require modification of variable residues to inhibit immunogenicity.

Turning now to the Office Action, the previous election is confirmed. New claims 37-48 all correspond to the elected invention, namely use of a Primatized® (chimeric) anti-CD4 antibody to treat autoimmune or non-immune diseases.

The previous objection to claims 22 and 28 based on improper dependency is moot in view of the cancellation of these claims.

Claims 17-21, 23-27 and 29-36 stand rejected under 35 U.S. §112 first paragraph based on lack of enablement and written description. The basis of the rejection was the Examiner's position that the specification does not sufficiently enable or describe anti-CD4 antibodies containing human constant regions and Old World Monkey variable regions for therapy, especially for non-autoimmune treatment. This rejection is respectfully traversed to the extent that it may be applicable to the claims as amended.

At the outset it is noted that the basis of the rejection relating to prevention of disease is moot. The current claims all are directed to treatment of a disease or condition associated with cytotoxic (CD4+) T lymphocytes.

As discussed at length in the specification, it is well established that many diseases or conditions are associated with cytotoxic T lymphocytes and further that these lymphocytes, if left untreated, can cause tissue destruction, inflammation, and other adverse cellular mediated immune responses. (See e.g., pages 1-3 of the specification). It is further demonstrated in the subject specification, as evidenced by the data in the examples, that chimeric antibodies according to the invention inhibit anti-CD4+ T cells and thereby function as immunosuppressants and inhibit unwanted T cell responses which are involved in disease pathology. Also, it has been established that the subject antibodies do not suffer from drawbacks of other prior chimeric antibodies, i.e., they are not immunogenic, do not elicit HAMA response, have a half-life comparable to human antibodies and retain human effector function. (See data in Examples of this application).

Thus, while the unpredictability associated with prior chimeric antibodies is acknowledged, (and cited as a basis for the rejection) the subject invention alleviates such problems, because of the intrinsic advantages of Primatized® antibodies. Also, Applicants respectfully traverse the position that undue experimentation would be required to practice the claimed invention. To the contrary, diseases associated with an increased number of circulating cytotoxic CD4+ T cells are well known, and it is reasonable to conclude that the subject chimeric antibodies will be beneficial in the treatment thereof, essentially based on their blocking the pathological effects associated with cytotoxic T cells, and based on their substantial absence of immunogenicity.

As evidence this fact, Applicants provide herein an article, Kon et al., The Lancet 352:1109-1113, which evaluates the clinical efficacy of a chimeric (Primatized®) anti-CD4 antibody according to the invention for the treatment of asthma (now specifically claimed). This is an example of a disease condition wherein disease pathogenesis involves an increased number of CD4 lymphocytes.

This clinical trial involves a single intravenous infusion of the chimeric anti-CD4 antibody to 22 asthma patients. This reference reports that there were no serious adverse events reported attributable to antibody infusion (See page 1111, left hand column, Results). Also, cytotoxic CD4 counts were reduced in all treated groups relative to the placebo.

Further, the researchers noted that this reduction was associated with a reduction in inflammation and a decrease in disease scores a relative to the placebo group. Therefore, these results support Applicants' claims, namely that the subject antibodies do not elicit an adverse immune response, that they inhibit CD4+ T cells, and that they may be used effectively treat conditions associated with such increased number of cells.

Based thereon, withdrawal of the §112 enablement and written description rejection is respectfully requested.

Also, previous claims 21 and 27 were separately rejected as requiring the use of a particular cell line, which allegedly should have been deposited in accordance with the deposit rules enumerated in 37 C.F.R. §1.802. This rejection is moot as no pending claims require the use of a specific cell line. To the contrary, where appropriate only certain claims refers to specific antibody sequences. Hence, no deposit is necessary for enablement as these antibodies could be synthesized based on sequence information in this application.

Finally, claims 17, 23 and 29 stand rejected as double patenting grounds. This rejection is traversed on the basis that none of the current pending claims are directed to treatment of rheumatoid arthritis. Also, a proper obviousness-double patenting requires 2-way obviousness. The treatment of rheumatoid arthritis specifically would not render obvious the treatment of any disease or condition associated with CD4+ T cells, or the specific diseases and conditions recited in the current pending claims.

Withdrawal of the double patenting rejection is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited.

Respectfully submitted,

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Attachments:
Appendix
Article (Kon et al., The Lancet 352:1109-1113)

APPENDIX

--37. A method of treating a patient having a condition or disorder characterized by an increased number of CD4 positive lymphocytes comprising administering a therapeutically effective amount of a chimeric anti-CD4 antibody that comprises Old World Monkey variable heavy and light regions and human constant regions, wherein said chimeric antibody inhibits CD4- positive dependent T cell responses.

38. The method of claim 37 wherein said disease or condition is transplant or graft-vs-host disease.

39. The method of claim 37 wherein said disease or condition is a non-autoimmune disease.

40. The method of claim 37 wherein said disease or condition is an allergic condition.

41. The method of claim 40 wherein said allergic condition is asthma.

42. The method of claim 37 wherein said chimeric anti-CD4 antibody has a human gamma 4 constant domain.

43. The method of claim 37 wherein said anti-CD4 antibody has a human gamma 1 constant domain.

44. The method of claim 42 wherein said gamma 4 constant domain has the amino acids at position 229 and 236 in the constant region respectively changed from a serine to a proline and a leucine to glutamatic acid.

45. The method of claim 37 wherein said Old World Monkey variable heavy and light regions are encoded by the DNA sequences having SEQ ID NO.: 3 and SEQ ID NO.: 1 respectively.

46. The method of claim 37 wherein said disease or condition is lymphoma.

47. The method of claim 37 wherein said disease or condition is an autoimmune disorder.

48. The method of claim 37 wherein said disease or condition is psoriasis.--

Early report

Randomised, double-blind, placebo-controlled study of chimeric antibody to CD4 (keliximab) in chronic severe asthma

Onn M Kon, Bhupinder S Sihra, Christopher H Compton, Thomas B Leonard, A Barry Kay, Neil C Barnes

Summary

Background There is substantial circumstantial evidence that CD4 lymphocytes have a role in the pathogenesis of chronic asthma. We investigated the efficacy and safety in severe corticosteroid-dependent asthma of a single intravenous infusion of keliximab (IDEC CE9.1), a chimeric monoclonal antibody to CD4.

Methods 22 patients were recruited from two asthma clinics. In an ascending-dose design, the first eight patients were assigned 0·5 mg/kg keliximab (six) or placebo (two); the next seven were assigned 1·5 mg/kg (five) or placebo (two); and the last seven were assigned 3·0 mg/kg (five) or placebo (two). Masked data on safety for each dose group were assessed before progression to the next dose. Patients kept a daily symptom diary and measured morning and evening peak expiratory flow (PEF) at home. PEF and forced expiratory volume in 1 s (FEV_1) were measured at follow-up clinic visits.

Findings Patients given 0·5 mg/kg or 1·5 mg/kg keliximab and placebo recipients did not differ in change from baseline of PEF, FEV_1, or symptom score. Those given 3·0 mg/kg keliximab differed significantly from placebo recipients in change in morning PEF (median area under curve [AUC] 445 *vs* −82·5, p=0·005) and evening PEF (median AUC 548 *vs* −85, p=0·014). Symptom score showed the same pattern (though differences did not achieve significance), but there was no difference in clinic FEV_1. There were no serious adverse effects related to treatment. Two patients had mild exacerbations of eczema and one developed a transient maculopapular rash. All doses of keliximab were associated with a reduction from baseline in CD4 count.

Interpretation Our findings raise the possibility that T-cell-directed treatment may be an alternative approach to the treatment of severe asthma.

Lancet 1998; **352**: 1109–13

Introduction

Asthma is characterised by bronchial inflammation with increased numbers of airway eosinophils and activated T lymphocytes.[1,2] The postulated causes of the mucosal damage and bronchial hyper-responsiveness are lipid mediators and basic proteins from eosinophils.[3] Eosinophil differentiation, maturation, endothelial adherence, activation, and degranulation are enhanced by the cytokines interleukin 5, interleukin 3, and granulocyte-macrophage colony-stimulating factor, all of which are produced by CD4 cells isolated from patients with asthma. CD4 T cells are an important source of these eosinophil-regulating cytokines;[4,5] furthermore, their numbers are increased in bronchoalveolar lavage fluid and bronchial biopsy samples from patients with asthma,[1,6] the cells are activated in acute and severe asthma,[7] and the numbers of cells correlate with eosinophil numbers and activation.[8,9]

The inflammatory changes in asthma have provided a mechanistic rationale for the clinical use of corticosteroids in treatment.[10] A small minority of patients with severe asthma remain poorly controlled despite oral corticosteroids. They suffer substantial morbidity related to the side-effects of their treatment. Immunosuppressants such as methotrexate,[11] oral gold,[11] and cyclosporin,[12] have therefore been investigated as steroid-sparing agents. An alternative approach is therapy with monoclonal antibodies, which allows specific cellular or mediator targeting. Therapy with monoclonal antibodies to CD4 has been investigated in other disorders associated with activated T lymphocytes.[13–17]

We have assessed in a randomised, placebo-controlled trial the safety and efficacy of a single dose of a chimeric human/macaque monoclonal antibody to CD4, keliximab (Primatized;[18] IDEC CE9.1; SmithKline Beecham, Harlow, UK), in patients with severe corticosteroid-dependent asthma.

Patients and methods

Patients

Patients were recruited from the London Chest Hospital and Royal Brompton Hospital. All patients met American Thoracic Society criteria for the diagnosis of asthma[19] and were receiving between 5 mg and 30 mg prednisolone daily. All had been on the lowest maintenance dose, which was kept constant for at least a month before randomisation to trial medication. They were all receiving high-dose inhaled corticosteroids (≥1000 μg daily) and additional appropriate asthma treatment as required. Each patient was maintained at the same dose of drugs except inhaled β_2-agonists throughout the study and run-in period. All patients were required to show an improvement of at least 15% in peak expiratory flow rate (PEF) or forced expiratory volume in 1 s (FEV_1) after inhaled salbutamol. In addition, they had to have a carbon monoxide transfer factor (TLCO) of more than 65%, to have smoked less than 10 pack-years, and not to be active smokers.

Reasons for exclusion were: possible contraindications to immunosuppressive therapy (including those who had received immunosuppressants in the preceding 3 months or those with a

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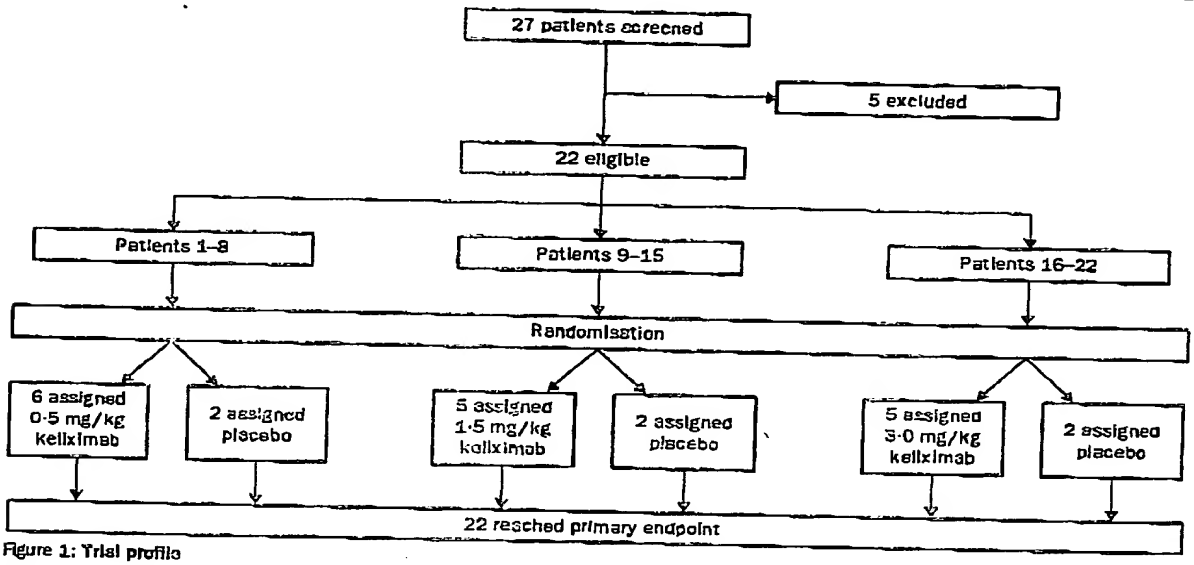

Figure 1: Trial profile

history of malignant disease, chronic hepatitis, or HIV infection); significant cardiopulmonary disease apart from asthma; recent (within 2 weeks) or current seasonal exacerbation of asthma or acute respiratory-tract infections; chronic pulmonary infections, allergic bronchopulmonary aspergillosis; pregnancy; lactation; and haematological or biochemical abnormalities. All patients gave written, informed consent to take part, and the study was approved by the ethics committees of the East London City and Hackney Health Authority and the Royal Brompton Hospital.

Design

In this dose-ranging study, three groups of patients were recruited. The dose of keliximab given was 0·5 mg/kg for group I, 1·5 mg/kg for group II, and 3·0 mg/kg for group III. In a randomised order, two patients within each group received placebo infusion (150 mL 0·9% saline). Therefore, a total of six patients received placebo. The randomisation schedule was produced by a random-number generator. Safety data from each group were reviewed, with allocation concealment maintained, before the higher-dose treatment was started. Because of this step and logistical constraints, the accrual period was 13 months.

After a run-in period of 1–2 weeks, each participant was randomly assigned keliximab (in the dose for the appropriate group) or 0·9% saline. Keliximab is an IgG_1 antibody with macaque variable regions and human constant regions. The macaque and human immunoglobulin sequences are highly conserved, so the antibody is of low immunogenicity.[9] The drug was dissolved in 150 mL 0·9% saline and given as a single intravenous infusion over 2 h. Patients were observed for 24 h after the infusion in hospital. The placebo and keliximab infusion bags were identical in appearance. Patients were then reassessed at 48 h and at 7, 14, and 28 days as outpatients. At each visit FEV_1 (Microlab 3000 vane anemometer) and PEF (mini-Wright peak-flow meter) were measured. At each visit CD4 and CD8 counts, complete differential blood-cell counts, biochemical profiles, and urine analysis were also done. The following directly conjugated monoclonal antibodies were used for three-colour flow-cytometric analysis of the peripheral blood: OKT8 fluorescein isothiocyanate, OKT4 phycoerythrin, and OKT3 energy-coupled dye. 100 µL volumes of peripheral whole blood in edetic acid were stained with the antibodies and incubated for 30 min. Red cells were removed by lysis. White cells were resuspended in 250 µL 0·5% formaldehyde in an isotonic buffer before analysis. The trial physician was not informed of CD4 counts after the initial screening visit.

Each participant was supplied with a mini-Wright peak-flow meter and kept a record of daily morning and evening PEF (best of three expiratory manoeuvres), a symptom score diary (an overall symptom score per day was calculated from the sum of daily overnight, morning, and daytime scores), and inhaled bronchodilator use for the trial period. With the exception of short-acting inhaled bronchodilators, use of all other medication was kept constant. Exacerbations of asthma during the trial were treated in a standard clinical way with an increase in prednisolone dose.

Statistical analysis

Primary outcome measures were the change from baseline of symptom score, FEV_1, and home PEF recordings. Secondary outcome measures were the outpatient PEF, diurnal variation in home PEF, and bronchodilator use. No formal sample-size

	Keliximab groups			Placebo recipients (n=6)
	0·5 mg/kg (n=6)	1·5 mg/kg (n=5)	3·0 mg/kg (n=5)	
Demography				
Age (years)	58 (39–69)	55 (43–66)	54 (47–59)	55 (35–68)
M/F	4/2	2/3	2/3	0/6
Disease duration (years)	29 (8–58)	38 (11–50)	28 (4–55)	33 (8–59)
Respiratory data				
FEV_1 (L)	1·47 (1·24–1·78)	1·16 (0·94–1·36)	1·55 (1·21–2·03)	1·33 (0·83–1·72)
FEV_1 (% predicted)	48 (35–60)	54 (39–58)	51 (44–61)	45 (33–59)
PEF (L/min)	176 (138–210)	133 (126–138)	185 (120–252)	141 (90–180)
Symptom score*	6·3 (4·6–8·6)	6·2 (5·0–7·0)	5·1 (2·0–6·8)	6·8 (3·0–8·8)
Treatment				
Prednisolone dose (mg/day)	14·8 (10–25)	8·0 (5–15)	11·5 (5–17·5)	16·4 (5–30)
Bronchodilator use (puffs/day)	7·83 (4·0–12·6)	6·56 (4·0–8·0)	9·12 (4·4–18·0)	8·45 (2·4–19·5)
Cell counts ($\times 10^6$/L)				
CD4	1280 (710–2110)	1370 (870–1760)	1480 (830–1630)	1500 (140–2740)
CD8	370 (130–560)	460 (110–860)	730 (320–1570)	510 (90–1100)

Data are mean (range) except M/F. *Mean of 5 days preceding treatment.

Table 1: Characteristics of patients at baseline

Adverse event	Keliximab groups			Placebo recipients (n=8)
	0·5 mg/kg (n=6)	1·5 mg/kg (n=5)	3·0 mg/kg (n=6)	
Headache	2	2	3	1
Asthma exacerbation	1	1	2	3
Haematuria (microscopic)	1	2	0	2
Upper respiratory-tract infection	0	1	1	3
Fatigue	1	0	3	0
Myalgia	1	0	1	2
Rash/exacerbation of eczema	0	1	2*	0
Anaemia	1	2	0	1
Back pain	1	0	0	1
Thirst	0	1	0	1

*One patient had a transient maculopapular rash.
Events for which there was only one occurrence among the 22 participants are not shown.

Table 2: Reported adverse events (in order of frequency)

calculation was done. The sample size of 22 was set at the beginning of the study because of the limitation on supply of the batch of antibody.

Statistical analysis was undertaken by an independent statistician with SAS for Windows version 6.12. For analysis of diary-card data, areas under the curve (AUC) of the change from baseline (mean of 5 days before infusion) was calculated for 1–14 days by the trapezoidal method. We chose to analyse the effects at days 0–14 and days 0–20 after initial examination of masked data. The data were summarised and tested for normality. Differences between the three keliximab groups and the placebo recipients were tested by parametric or non-parametric one-way ANOVA. When significant variation was found, it was further investigated by means of all pairwise comparisons of the least-squares means.

For analysis of clinical and laboratory data, the variation over time within each group was tested with two-way ANOVA and, if significant, the change from baseline was then tested by a paired *t* test. Differences in the changes from baseline among the three keliximab groups and the placebo recipients were tested by one-way ANOVA and, if significant, by all pairwise comparisons of the least-squares means.

Results

We screened 27 asthmatic patients, dependent on oral corticosteroids and attending the London Chest and Royal Brompton Hospital chest clinics (figure 1). 22 met entry criteria and consented to take part in the study (table 1). All patients completed the assessments during the trial period and there were no withdrawals from the study protocol.

There were no serious adverse events related to infusion of keliximab. Two participants (one in the 1·5 mg/kg group and in one in the 3·0 mg/kg group) developed mild exacerbations of pre-existing atopic eczema 48 h after infusion (treated with topical hydrocortisone and antihistamines). One participant in the 3·0 mg/kg group developed a generalised pruritic maculopapular eruption 24 h after the infusion (treated with oral antihistamines alone). There were no opportunistic infections reported in any of the keliximab groups. Adverse experiences reported by patients are shown in table 2. Biochemical screening showed no deterioration in hepatic or renal function and there were no episodes of leucopenia or thrombocytopenia. There were three exacerbations of asthma among the placebo recipients, one in each of the 0·5 mg/kg and 1·5 mg/kg keliximab groups, and two in the 3·0 mg/kg keliximab group. Prednisolone dose was increased because of exacerbations in two placebo recipients 2 weeks after

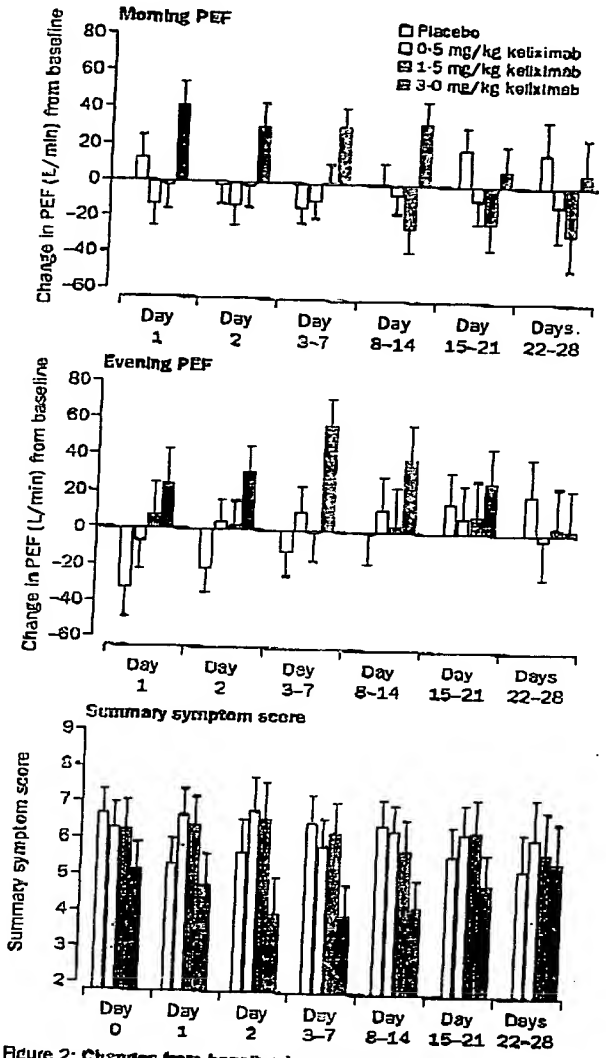

Figure 2: Changes from baseline in morning and evening PEF and total symptom score
For days 3–7, 8–14, 15–21, 22–28, mean change for relevant period is given. Error bars=SE.

infusion and in two patients in the 3·0 mg/kg keliximab group at the 4-week visit.

There was significant variation between the groups in the AUC of changes from baseline for both morning and evening PEF ($p=0·0174$ and $p=0·05$). These improvements were confined to the 3·0 mg/kg keliximab group, in which the changes from baseline to day 14 in morning and evening PEF were significantly greater than those in the placebo group (figure 2, $p=0·005$ and $p=0·014$ respectively). The median AUCs for morning and evening PEF were substantially greater for the 3·0 mg/kg keliximab group than for the placebo group (table 3). The improvement in PEF with 3·0 mg/kg keliximab was apparent by 24 h, and began to decline only after the 2-week follow-up visit (figure 2).

This pattern was reflected in the trend for improvement in summary symptom scores in the

Group	Change from baseline (days 1–14 AUC)	
	Mean (SD)	Median (range)
Morning PEF		
0·5 mg/kg (n=6)	73·5 (453·9)	29·5 (−601 to 795)
1·5 mg/kg (n=5)	−186·1 (159·8)	−141 (−405 to −13)
3·0 mg/kg (n=5)	491·4 (421·6)	425 (−80 to 1059)
Placebo (n=6)	−155·0 (101·8)	−82·5 (−305 to 69)
Evening PEF		
0·5 mg/kg (n=6)	−92·5 (510·7)	33 (−570 to 274)
1·5 mg/kg (n=5)	57·1 (281·1)	−46 (−129 to 544)
3·0 mg/kg (n=5)	633·6 (697·2)	648 (−315 to 1624)
Placebo (n=6)	−62·2 (200·2)	−85 (−351 to 284)

Table 3: Summary of changes in PEF for days 1–14

3·0 mg/kg keliximab group (figure 2); the mean AUC of change from baseline for days 0–14 was −13·1 compared with −5·0 for the placebo recipients. There was, however, no significant variation between the groups in changes from baseline in the summary symptom score (p=0·5). There was no significant change in clinic FEV_1 but the placebo recipients' clinic PEF at day 2 differed significantly from that of the 1·5 mg/kg (p=0·023) and 3·0 mg kg keliximab groups (p=0·041).

Inhaled bronchodilator use was similar in all four groups at baseline (table 1), and there were no significant changes from baseline in any of the groups for days 1–14.

Peripheral blood CD4 counts were significantly lower than baseline in all three keliximab groups but not in the placebo recipients (figure 3). The CD4 count no longer differed significantly from baseline values by 2 days in the 0·5 mg/kg keliximab group and 7 days in the 1·5 mg/kg group but remained significantly lower than baseline until 14 days in the 3·0 mg/kg group. There was no significant variability in CD8 counts among treatment groups and placebo recipients. Blood eosinophil and monocyte counts were not affected by treatment with the antibody (data not shown).

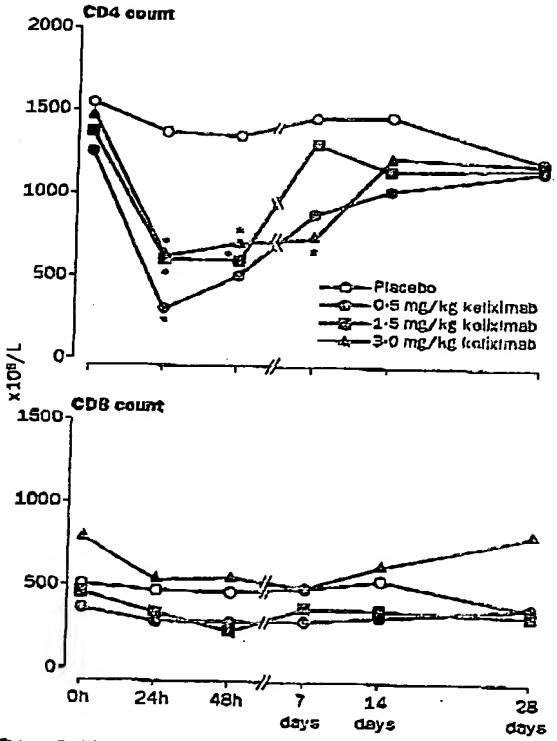

Figure 3: Change in CD4 and CD8 counts (×10⁶/L) from baseline
*Significantly different (p≤0·05) from baseline.

Discussion

In this trial of a monoclonal antibody against CD4 in patients with chronic severe asthma, the patients who received the highest dose of the antibody (3·0 mg/kg) had a significant increase in morning and evening PEF recordings compared with placebo. These changes were accompanied by a decrease in symptom scores, although it did not reach statistical significance.

Apart from clinic PEF measurements at day 2, lung function measured at the clinic showed no significant changes. This finding may reflect difficulties with standardisation of conditions for the clinic visits, since many of the participants were unable to refrain from using their bronchodilators for the 6 h before the clinic time. This effect is not a confounding factor in the twice-daily home recordings. The increase in oral corticosteroid requirements at 2–3 weeks after infusion of placebo in two patients may explain the apparent improvements in home PEF in the placebo group during weeks 3–4 (figure 2). There were four exacerbations in the keliximab groups; two patients in the 3·0 mg/kg cohort required an increase in oral corticosteroids, but these were initiated only at the final visit and would therefore not influence the changes seen during days 0–14. Similarly, although use of short-acting inhaled β_2-agonists was allowed, it was similar in all groups with no changes after infusion.

No serious adverse effects or cytokine release syndrome[20] were observed. The exacerbation of eczema in two participants and the generalised rash in one individual required only topical treatment or antihistamines. Minor events judged to be possibly related to the antibody treatment include headache, fatigue, arthralgia, and pseudogout. There were three episodes of transient microscopic haematuria in the keliximab cohorts and two in the placebo group but no red-cell casts were detected at any time. Anti-idiotypic antibodies were not detectable in any of the keliximab groups at 4 weeks after infusion.

Reductions in CD4 counts at 24 h were similar in all three keliximab groups, but there was a dose-related effect in the time that the CD4 counts were significantly lower than baseline. The CD4 count was low for longest in the 3·0 mg/kg group, which may help to explain the improvement seen in this group.

These findings further implicate CD4 T lymphocytes in severe asthmatic inflammation and are consistent with previous findings on the T-lymphocyte selective agent cyclosporin.[12] An effect on other inflammatory cells with detectable CD4 molecules such as monocytes,[21] dendritic cells,[22] and eosinophils[23] cannot be excluded, although there were no changes in peripheral-blood eosinophil and monocyte counts after infusion.

There were no serious adverse events attributable to treatment. Previous studies of monoclonal antibody treatment against CD4 in rheumatoid arthritis, even with long-term depletion of CD4 lymphocytes and in combination with other immunosuppressant therapy,

have not shown any significant increase in the risk of opportunistic infections or neoplasms,[24] but the use of these agents in asthma would require a careful assessment of the risk-benefit ratio in each patient. At present, specific targeting of CD4 lymphocytes by monoclonal antibodies should be regarded as experimental therapy but may represent a useful adjunctive treatment in the management of severe asthma.

Contributors

Oon Min Kon was responsible for recruitment and execution of the study, and provision of clinical data. Bhupinder Sihra carried out and analysed flow-cytometry. Christopher Compton and Thomas Leonard participated in the study design and advised on data analysis and interpretation. Barry Kay and Neil Barnes created the idea and design of the study and supervised the clinical and laboratory aspects. All investigators contributed to the writing of the paper.

Acknowledgments

We thank the patients who participated in the trial and their referring physicians, Jackie Turner for statistical services, S Segbedzi and the pharmacy staff, L John and the lung-function staff, and A Joshi, J McRae, J Mitchell, C Ramsay, C A Shaw, and H Whitelegg for their help during the study.

This study was funded by SmithKline Beecham Pharmaceuticals.

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